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INFECTIVE ENDOCARDITIS DIAGNOSIS ANTIMICROBIAL THERAPY AND MANAGEMENT

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ABSTRACT

Infective Endocarditis (IE) is the inflammation of inner heart tissue and its valves, caused by infecting micro-flora. The median age of patients has increased from 30 years to currently 57.9 years. The disease is uncommon in children unless associated with cardiac defects, surgical procedures or nosocomial catheter related bacteremia. The characteristic lesion of IE is the vegetation, amorphous mass of platelets and fibrin with dense bacteria, and inflammatory cells enmeshed. In IE infecting organisms are viridans group of Streptococci, *Streptococci*, Staphylococci, HACEK group of organisms and fungi. Diagnosis of IE is by modified Duke Criteria, evidence of infecting bacteria and evidence of endocarditis by two dimensional echocardiography .Treatment of IE with IV bactericidal antibiotics, penicillin, ceftriaxone and an amino glycoside added for Enterococci. Fungal infection may be treated with amphotericin and flucocytosine. IE may be associated with high mortality.

KEYWORDS: Infective Endocarditis, *Streptococci*, Duke Criteria, Antibiotic Therapy

INTRODUCTION

Infective Endocarditis (IE) is the inflammation of the heart valve due to infection. The term infective endocarditis was first used by Thayer and later popularized by Lerner and Weinstein, is preferable to old term *bacterial endocarditis*, because chlamydiae , rickettsiae, mycoplasma, fungi, and even viruses may be responsible for the syndrome [1]. The mean annual incidence of IE was 5 to 7 cases per 100,000, person-years from 1970 to 2000. A similar figure of 1.7 per 100,000, was reported from a prospective survey in Louisiana, analogous to results from United Kingdom and from France[2,3].The median age of patients with IE has increased from younger than 30 years in 1926 to currently patients older than 50 years[4]. In a recent report, amomg more than 2700 patients from 58 centers in 25 countries with definitive IE by the modified Duke criteria, the median age was 57.9 years[4].The disease is uncommon in children unless is associated with (a)congenital heart disease,(b) surgical repairs of these defects,(c) nosocomial catheter –related bacteremia, especially in infants[5]. A new form of the disease, health care –associated IE, has emerged secondary to the introduction of new therapeutic modalities (e.g. intravenous (IV) catheters ,hyper alimentation lines, pacemakers, dialysis shunts)[6]. The characteristic lesion of IE is the vegetation, a variably sized amorphous mass of platelets and fibrin in which a dense population of bacteria and a few inflammatory cells are enmeshed [7]. Bacteremia allows the conversion of the sterile thrombus to a vegetation .Increased risk of bacteremia occurs in the presence of mucosal surface, especially the infected one and the procedures involving genitourinary tract and the gastrointestinal tract [8].Diagnosis of IE is by modified Duke and von Reyn criteria[9]. Micro-organisms responsible for IE are mainly *Streptococci*, (55%), *Staphylococci*, (35%). Miscellaneous organisms (10%) that include includ: HACEK organisms (*Haemophilus, Acinomyces. Cardiobacterium, Ekkenella,Kingnella*). Demonstration of infecting organisms is by microbiologic methods and evidence of endocarditis by two dimensional echocardiography (2D echo) used across the chest wall (transthoracic echo or TTE)[10]. This paper reviews, clinical presentation, pathogenesis, diagnosis and treatment of IE.

INFECTIVE ENDOCARDITIS

Clinical Manifestations

Fifty- five percent to 75 % of patients with IE of native valves have predisposing conditions, including rheumatic heart disease, congenital heart disease, mitral valve prolapse, degenerative heart disease, asymmetric septal hypertrophy, or intravenous heart disease (i.v.) drug abuse[11]. AS the population at risk has been increasing in recent decades, rheumatic heart disease has become a less important predisposing condition, accounting for fewer than 20 % of cases [12]. Mitral valve prolapse accounts for 7 % to 30 % of IE in native valves not related to drug abuse or nosocomial infection. Increased risk of IE in patients with mitral valve prolapse occurs in those with both prolapse and a mitral regurgitation murmur[13]. A substantial number of cases of nosocomial endocarditis associated with bacteremia from i.v. catheters, postoperative wound infections, genitourinary manipulation, hyper alimentation lines, and hem dialysis shunts have been described in patients with hospitalized or treated for a variety of other illnesses [14].

The presenting signs and symptoms of bacterial endocarditis (BE) are variable and nonspecific. The possibility this diagnosis should be considered whenever a patient presents with fever of more than several days' duration with no other apparent cause and in association with a significant heart murmur. The type of clinical presentation can have practical implications with regard to probable bacterial etiology and the degree of urgency in instituting therapy; it is therefore useful to attempt to classify suspected BE as **acute or sub-acute** [15].

The interval between an event likely to produce high grade bacteremia (e.g. dental extraction) and the onset of symptoms of IE, contrary to older estimates, is quite short. The so called incubation period in 84 % of 76 cases of *streptococci* of IE was less than 2 weeks. On the other hand, the time from onset of symptoms to diagnosis in the sub-acute form of IE is quite long, with median interval of approximately 5 weeks. Symptom duration of cases managed in community hospitals is shorter than patients referred to tertiary care center, reflecting a referral bias [16, 17].

Historically, infective endocarditis has been clinically divided into acute and sub-acute presentations because untreated patients tended to live longer with sub-acute as opposed to the acute form). This classifies both the rate of progression and severity of disease[18] *Sub- acute bacterial endocarditis* (SBE) is often due to *Streptococci* of low virulence and mild to moderate illness which progress slowly by over weeks and months and has low propensity to hemotogenously seed extra cardiac sites. *Acute bacterial* endocarditis (ABE) is a fulminant illness over days to weeks, and is more likely due to *Staphylococcus aureus* which has much greater virulence, or disease producing capacity and frequently causes metastatic infection [18]. This classification is now discouraged because the ascribed associations (in terms of organism and prognosis) were not strong enough to be relied upon clinically. The *short incubation* (meaning less than six weeks) and *long incubation* (greater than about six weeks) are preferred [19].

Signs and Symptoms

The presenting signs and symptoms off BE and IE are variable and often nonspecific that include:

Fever occurs in 97 % of people; malaise and endurance fatigue in 90% of people

A new or changing heart murmur, weight loss, and coughing occur in 35 % of people.

Vascular Phenomena

Septic embolism (causing thromboembolic problems such as stroke in parietal lobe of the brain or g angrene of fingers), Janeway lesions (painless hemorrhagic cutaneous lesions on palm and soles), intracranial hemorrhage, conjunctiva hemorrhage, splinter hemorrhages, renal infracts, and splenic infracts.

Immunologic Phenomena

Glomerulonephritis which allows for blood and albumin to enter the urine. Osler's nodes (painful subcutaneous lesions in distal fingers), Roth's spots on the retina, positive serum rheumatoid factor. Other signs may include; night sweats, rigors, anemia, splenomegaly.

Cause of Presenting Signs

In the past, bacteremia caused by dental procedures (in most cases due to streptococci viridians, which resides in oral cavity), such as a cleaning or extraction of a tooth was thought to be more clinically significant than it actually was. However, it is important that a dentist or a dental hygienist be told of any heart problems before commencing treatment.

Antibiotics are administered to patients with certain heart conditions as a precaution, although this practice has changed in the US, with new American Heart Association guidelines released in 2007, and in the UK as of March 2008 due to NICE guidelines [21]. Everyday tooth brushing and flossing will similarly cause bacteremia. Although there is little evidence to support antibiotic prophylaxis for dental treatment, the current American Heart Association guidelines are highly accepted by clinicians and patients [22,23].

Other conditions that result in high number of bacteria entering into the bloodstream include Colorectal cancer (mostly *streptococcus bovis*), serious urinary tract infections (mostly *enterococci*), and drug injection (*Staphylococcus aureus*). with a large number of bacteria, even a normal heart valve may become infected [24].

A more virulent organism (Such as *Staphylococcus aureus*) can cause infective endocarditis by infection even a normal heart valve. Intravenous drug users tend to get their right-sided heart valve infected because the veins that are injected drain into the right side of the heart. In rheumatic heart disease, infection occurs on the aortic and mitral valves on the left side of the heart. Other factors that increase the risk of developing IE are low level of blood cells, in immunodeficiency or immunosuppression, malignancy, diabetes, and alcohol [18].

PATHOGENESIS

Endothelial Damage: The hydrodynamic leading to endothelial damage include the impact of a high velocity jet flow from a high to low pressure chamber, and high velocity flow across a narrow orifice. A platelet and thrombus complex forms at the site in response to the damage. It is the same location as this sterile thrombus formation that principles of hydrodynamics also allow the maximum deposition of bacteria during bacteremia, that is, just beyond the low-pressure side of the orifice, or at the site of jet stream impact on the endothelium. IE is uncommon in association of low-pressure flow abnormalities such as an isolated atrial septal defect or mitral stenosis[7].

Bacteremia: Bacteremia allows the conversion of the sterile thrombus to vegetation. Bacteremia rates are highest for events that traumatize the oral mucosa, especially gingiva, and progressively decrease with procedures involving genitourinary tract and gastrointestinal tract. A further increased risk of bacteremia occurs in the presence of a diseased mucosal surface, especially an infected one[8].

Bacterial Factors: Bacterial adherence to thrombus is critical in order for infection to occur. Multiple factors that enhance adherence, including the ability to produce dextran, cause aggregation of platelets, and bind to fibronectin, appear to be important for most of the gram-positive organisms that commonly cause IE. Resistance to host defense mechanisms is also pivotal. The ability of many gram-negative bacilli to cause IE is limited by complement-mediated bactericidal activity of serum [7].

Intact Endothelium: *Staphylococcus aureus* is the most common gram positive organism of ABE able to infect intact vascular endothelium. The response for this are incompletely understood.

DIAGNOSIS

The von Reyn criteria established in 1981 to assist in diagnosis of infective endocarditis have largely been replaced the now well-accepted Duke criteria which have recently been modified by Li et al [25,9]. Duke criteria rely heavily on the results of echocardiography, research has addressed when to order an echocardiogram by using signs and symptoms to predict occult endocarditis among patients with intravenous drug abuse[26-28] and among non-drug-abusing patients [29,30].

Non-Drug-Abuser Patients, there is less 5 % chance of occult endocarditis. Mellors in 1987 found no cases of endocarditis nor Staphylococcal bacteremia among febrile patients in emergency room[30]. The upper confidence of 135 is 5 %, so for statistical reasons alone, there is up to a 5% chance of endocarditis among these patients. In contrast, Leibovici found that among 113 non-selected adults admitted to the hospital because of fever there was two cases (1.8% with 95 % CI: 0% to 7%) of endocarditis [29].

Intravenous Drug-Abuser Patients, there is about 10% to 15% prevalence of endocarditis. This estimate is not substantially changed by whether the doctor believes the patient has a trivial explanation for fever [28]. Weisse found that 13 % of 121 patients had endocarditis[26]. Marantz also found a prevalence of endocarditis of 13% among such patients in the emergency room with fever [28]. Samet found a 6% incidence among 283 such patients, but after excluding patients with initially apparent major illness to explain (including 11 cases of manifest endocarditis), there was a 7% prevalence of endocarditis[27].

Echocardiography, The transthoracic echocardiogram has a sensitivity and specificity of approximately 65% and 95% if the echo cardiographer believes there is 'probable' evidence of endocarditis [31,32].

Modified Duke Criteria, was established in 1994 and revised in 2000, the criteria are collection of major and minor criteria used to establish a diagnosis [26, 27, rept]. Modifications shown in italics.

Major Criteria

Blood culture positive for IE, typical microorganisms consistent with IE from two separate blood cultures: Viridans S*treptococcus bovis* HACEK group, *Staphylococcus aureus or*

Community- acquired *enterococci*, in the absence of a primary focus; *or*

Microorganisms consistent with IE from persistently positive blood cultures, defined as:

At least 2 positive cultures of blood samples drawn >12h apart; *or*

All 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 hr. apart)

Single blood culture positive for Coxxiellaburnetti or anti-phase I IgG antibody titer >1:800

Evidence of Endocardial Valve Involvement

Endocardigram positive for IE *(TEE recommended in patients with prosthetic valves, rated at least "positive IE by clinical criteria, or complicated IE (paravalvular abscess); TEE as first test in other patients)*, defined as follows:

Oscillating intracardiac mass on valve or implanted material in the absence of an alternative anatomic explanation, *or*

Abscess; *or*

New partial dehiscence of prosthetic valves

New vulvar regurgitation (worsening or changing or persisting murmur not sufficient)

Minor Criteria

Predisposition, predisposing heart condition or injection drug user Fever, temperature>38C

Vascular Phenomena: major arterial emboli, septic pulmonary infarcts,

mycoticaneurysm, intracardialhemorrhage,conjunctivalhemorrhage,andJaneway lesions

Immunologic, phenomena: glomerulonephritis, oslernodes, Ruth spots, and rheumatoid factor

Microbiological Evidence: positive blood culture but does not meet a major criterion as above[b]

Or serologic evidence of active infection with organisms consistent with IE *Echocardiograhic minorcriteria eliminated*

[b]Excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

INFECTING MICRO-FLORA

Infective endocarditis is caused by many organisms. Old term bacterial endocarditis has been replaced by IE because, Chlamydia, Rickettsia, fungi and viruses may cause the syndrome. The main infecting micro-flora causing IE includes:

Streptococci account for approximately 55% of all cases of native vulvar BE in the non-addict population ***Streptocciviridans*** the single most common organism cause 35% of the cases. Approximately 10% cases are caused by ***enterococci***. Another 10% are caused by other nonhemolytic, microerophilic, anaerobic or nonenterococcal group D Streptocicci.Group A B hemolytic Streptococci are a rare cause[7].

Staphylococci account for approximately 35% of cases. Most ***Staphylococci*** causing BE are coagulase- positive. Coagulase- negative ***Staphylococc***i are common in prosthetic valve endocarditis but infrequently cause disease on native valves [7].

Miscellaneous organisms account for 10% cases this includes HACEK organisms (*Haemophilus, Actinomyces,Cardiobacterium,Eikenella,Kingella*), *Pseudomona*s, gram negative enteric bacilli [33,34] *Pneumococci*, and gonococci. Reports can be found of endocarditis caused by any bacterium [7,35,36]. *Candida albicans*, a yeast, is associated with endocarditis in IV drug users and immunocompromisedpatients. Other fungi demonstrated to cause endocarditis are *Histoplasmacapsulatum*and *Aspergillus*. Endocarditis with *Tricosporonasahii* has been reported in a case report [37,38].

ANTIMICROBIAL THERAPY AND MANAGEMENT

In acute endocarditis due to the fulminant inflammation empirical antibiotic therapy is started immediately after the blood has been drawn for culture. This usually includes vancomycin and ceftriaxone IV infusions until the microbial

identification and susceptibility report with the inhibitory concentration becomes available following modification of the antimicrobial therapy to target the specific microorganism. It should be noted that routine use of gentamicin to treat endocarditis has fallen out of favor due to lack of evidence to support its use (except in infections caused by *Enterococus* and nutritionally variant *Streptococci*) and the high rate of complications [39].

The most common organisms responsible for infective endocarditis is *Staphylococcus aureus,*which is resistant to Penicillin in most cases. High rate of resistant to Oxicillin are also seen, in which cases treatment with vancomycin is required [40].Viridans group *Streptococci* and *Streptococci Bovis* are usually highly susceptible to penicillin and can be treated with penicillin or ceftriaxone [41,WP,30]. Relatively resistant strains of viridans*Streptococc*i and *Streptococcus bovis* are treated with penicillin or ceftriaxone along with a short 2 week course of aminoglycoside during the initially phase of treatment[41,rept]. Highly penicillin resistant strains of viridans group *Streptococci*, nutritionally variant *Streptococc*i like *Granulicatellasp.*,*Gemellasp*. and *Abiotrophiadefectiva*, and *Enterococc*i are usually treated with a combination therapy consisting of penicillin and a aminoglycoside for the entire duration of 4-6 weeks[41].

Selected patients may be treated with a relatively shorter course of treatment (2weeks)[41], with benzyl penicillin IV if infection is caused by viridans group of *Streprtococcusbovis* as long as the following conditions are met: (a) Endocarditis of a native valve, not of a prosthetic valve,(b) An MIC≥0.12mg/l,(c) Complications such as heart failure, arrhythmia and pulmonary embolism occur, (d) No evidence of extra cardiac complication like septic thromboembolism,(e) No vegetation >5mm in diameter conduction defects,(f) Rapid clinical response and clearance of blood stream infection. Fungal endocarditis requires a combined chemotherapeutic and surgical approach. Amphotericin B is administered 0.5mg/kg/day. Most *Candida* and *Torulopsis* species are sensitive to flucytosine, and 150mg/kg/day orally may added to amphotericin; flucytosine, however, should not be used alone [42, AP59]. In IE high dose bactericidal antibiotics are administered for 4- 6 weeks, patients infected with sensitive organisms are given shorter course of therapy. Surgery may be indicated in patients with prosthetic valve endocarditis, uncontrolled infection or cardiac failure.

CONCLUSIONS

IE is infection of cardiac valves, it is mainly bacterial in certain cases fungal. Most common causative organisms are *Streptococci, enterococci, Staphylococci*,gram negative bacteria and *Candida* species. Presenting symptoms are due to valve and heart damage, bacteremia, fever and glomerulonephritis. Evidence of IE is by blood cultures and echocardiogram. Long term treatment with highdose antibiotics. Surgery may be necessary in persistent infection.

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